

S/N 09/855,458  
Page 2 of 20

### **AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

### **LISTING OF CLAIMS**

1. (currently amended) A method comprising:  
generating a model of a biological system, the model comprising rules that express a substitution of at least one symbol by at least another symbol, the symbols representing a biological element, at least some of the rules representing interactions between biological elements, and at least some of the rules being expressed in a manner that enables an inference engine to process the rules by substituting symbols and infer alternative results from the system based on symbols representing an initial hypothetical state.
2. (original) The method of claim 1 wherein one or more of the rules comprises an operator for expressing a relationship between at least two of the biological elements, the operator conforming to associative and commutative properties.
3. (original) The method of claim 1 wherein one or more of the rules expresses concurrent state transitions.
4. (currently amended) A method comprising:  
generating a model of a biological system, the model comprising rules that express a substitution of at least one symbol by at least another symbol, the symbols representing a biological element, ~~The method of claim 1~~ wherein at least some of the rules are not terminating and at least some of the rules are expressed in a manner that enables an inference engine to infer alternative results from the system based on an initial hypothetical state.

S/N 09/855,458

Page 3 of 20

5. (original) The method of claim 1 wherein at least one of the rules represents a feedback or feedforward interaction between biological elements.
6. (original) The method of claim 1 wherein one or more of the rules is reflective.
7. (original) The method of claim 1 wherein one or more of the symbols representing the biological elements is typed.
8. (original) The method of claim 7 wherein the types of symbols are organized in hierarchical classes.
9. (currently amended) A method comprising:  
generating a model of a biological system, the model comprising rules that express a  
substitution of at least one symbol by at least another symbol, the symbols representing  
a biological element, and at least some of the rules being expressed in a manner that  
enables an inference engine to process the rules by substituting symbols and infer  
alternative results from the system based on an initial hypothetical state, wherein one or  
more of the symbols are typed into hierarchical classes, and ~~The method of claim 8~~  
wherein a symbol for one of the hierarchical classes is matched by any symbol that is a member of the hierarchical class.
10. (original) The method of claim 1 wherein at least some of the rules are conditional.
11. (original) The method of claim 1, further comprising expressing the rules graphically by representing at least some of the symbols as points and at least some of rules as lines interconnecting points, each interconnected point corresponding to a symbol that is an operand of the rule.

S/N 09/855,458

Page 4 of 20

12. (withdrawn) The method of claim 1 wherein one or more of the symbols represents a polypeptide selected from the group consisting of a protein kinase, a transcription factor, a cytokine, and a nucleotide binding protein.
13. (withdrawn) The method of claim 1 wherein one or more of the symbols represents a polypeptide selected from the group consisting of pRB, cyclins, cyclin-dependent kinases, cyclin-dependent kinase inhibitors, p53, E2F, and DP 1.
14. (original) The method of claim 1 wherein one or more of the symbols represents a drug or exogenous agent.
15. (withdrawn) The method of claim 1 wherein one or more of the symbols represents post-translational modification.
16. (original) The method of claim 1 wherein the model of the biological system includes a first set of symbols representing molecules in a first cell and a second set of symbols representing molecules in a second cell.
17. (original) The method of claim 16 wherein one or more of the first set of symbols comprises the same symbols of the second set.
18. (currently amended) An article comprising machine-readable media having encoded thereon a model of a biological system, the model comprising rules that express a substitution of at least one symbol by at least another symbol, the symbols representing a biological element, and at least one of the rules being expressed in a manner that enables an inference engine to process the rules by substituting symbols and infer alternative results from the system based on symbols representing an initial hypothetical state.

S/N 09/855,458

Page 5 of 20

19. (original) The article of claim 18 wherein one or more of the rules comprises an operator for expressing a relationship between at least two of the biological elements, the operator conforming to associative and commutative properties.
20. (original) The article of claim 18 wherein one or more of the rules expresses concurrent state transitions.
21. (original) The article of claim 18 wherein at least some of the rules are not terminating.
22. (original) The article of claim 18 wherein at least one of the rules represents a feedback or feedforward interaction between biological elements.
23. (original) The article of claim 18 wherein one or more of the rules is reflective.
24. (original) The article of claim 18 wherein one or more of the symbols representing the biological elements is typed.
25. (original) The article of claim 24 wherein the types of symbols are organized in hierarchical classes.
26. (original) The article of claim 25 wherein a symbol for one of the hierarchical classes is matched by any symbol that is a member of the hierarchical class.
27. (original) The article of claim 18 wherein at least some of the rules are conditional.
28. (withdrawn) The article of claim 18 wherein one or more of the symbols represents a polypeptide selected from the group consisting of a protein kinase, a transcription factor, a cytokine, and a nucleotide binding protein.

S/N 09/855,458

Page 6 of 20

29. (withdrawn) The article of claim 18 wherein one or more of the symbols represents a polypeptide selected from the group consisting of pRB, cyclins, cyclin-dependent kinases, cyclin-dependent kinase inhibitors, p53, E2F, and DPi.
30. (original) The article of claim 18 wherein one or more of the symbols represents a drug or exogenous agent.
31. (withdrawn) The article of claim 18 wherein one or more of the symbols represents post-translational modification.
32. (currently amended) An article comprising machine-readable media having encoded thereon a model of a biological system, the model comprising rules that express a substitution of at least one symbol by at least another symbol, the symbols representing a biological element, and at least one of the rules being expressed in a manner that enables an inference engine to infer alternative results from the system based on an initial hypothetical state ~~The article of claim 18~~ wherein the model of the biological system includes a first set of symbols representing molecules in a first cell and a second set of symbols representing molecules in a second cell.
33. (original) The article of claim 32 wherein one or more of the first set of symbols comprises the same symbols of the second set.
34. (original) A method comprising:  
receiving a set of symbols in an inference engine, the set representing a hypothetical initial state of a biological system, the symbols representing elements of the biological system; and  
processing the initial state using rules that express a substitution of at least one of the symbols by at least another symbol representing a biological element to infer alternative resultant states of the system.

S/N 09/855,458

Page 7 of 20

35. (original) The method of claim 34 wherein the set of symbols representing the hypothetical initial state is generated from an expression profile for a biological sample.
36. (original) The method of claim 34, further comprising: parsing a profile for a biological sample into symbols; and include at least some of the symbols in the set of symbols representing a hypothetical initial state of the biological system.
37. (original) The method of claim 36 wherein the profile is a gene expression profile.
38. (withdrawn) The method of claim 36 wherein the profile is a polypeptide profile.
39. (original) The method of claim 36 wherein the biological sample is associated with a disease or disorder.
40. (original) The method of claim 39 wherein the disease or disorder is selected from the group consisting of cancer, diabetes, infection by a pathogen, inflammation, and a disease of aging.
41. (original) The method of claim 34 wherein infinite substitution chains are detected.
42. (original) The method of claim 34 wherein values of one or more of the symbols of the resultant states are displayed graphically as a wiring diagram.
43. (original) The method of claim 42 wherein the wiring diagram comprises a graph having lines interconnecting points, each line corresponding to a rule such that each interconnected point of the line corresponds to a symbol that is an operand of the rule.

S/N 09/855,458  
Page 8 of 20

44. (original) The method of claim 34, further comprising: comparing each of the alternative resultant states to one or more reference states.
45. (original) The method of claim 44 wherein the one or more reference states comprise a state associated with cell proliferation, cell quiescence, cell apoptosis, and cell differentiation.
46. (original) The method of claim 44 wherein the alternative resultant states are compared to two or more reference states, each reference state being associated with a diagnosis.
47. (original) The method of claim 44 wherein the hypothetical initial state represents a sample from a patient.
48. (original) The method of claim 34 wherein the set of symbols representing hypothetical initial state comprises a symbol representing a genetic alteration.
49. (original) The method of claim 44 wherein the one or more reference states comprise a state associated with a disease or disorder.
50. (original) The method of claim 49 wherein the disease is selected from the group consisting of cancer, diabetes, infection by a pathogen, inflammation, and a disease of aging.
51. (original) The method of claim 34 wherein one or more of the rules comprises an operator for expressing a relationship between at least two of the biological elements, the operator conforming to associative and commutative properties.
52. (original) The method of claim 34 wherein one or more of the rules expresses concurrent state transitions.

S/N 09/855,458

Page 9 of 20

53. (original) The method of claim 34 wherein at least some of the rules are not terminating.
54. (original) The method of claim 34 wherein at least one of the rules represents a feedback or feedforward interaction between biological elements.
55. (original) The method of claim 34 wherein one or more of the rules is reflective.
56. (original) The method of claim 34 wherein one or more of the symbols representing the biological elements is typed.
57. (original) The method of claim 56 wherein the types of symbols are organized in hierarchical classes.
58. (original) The method of claim 57 wherein a symbol for one of the hierarchical classes is matched by any symbol that is a member of the hierarchical class.
59. (original) The method of claim 34 wherein at least some of the rules are conditional.
60. (withdrawn) The method of claim 34 wherein one or more of the symbols represents a polypeptide selected from the group consisting of a protein kinase, a transcription factor, a cytokine, and a nucleotide binding protein.
61. (withdrawn) The method of claim 34 wherein one or more of the symbols represents a polypeptide selected from the group consisting of pRB, cyclins, cyclin-dependent kinases, cyclin-dependent kinase inhibitors, p53, E2F, and DP 1.



S/N 09/855,458

Page 10 of 20

62. (original) The method of claim 34 wherein one or more of the symbols represents a drug or exogenous agent.
63. (withdrawn) The method of claim 34 wherein one or more of the symbols represents post-translational modification.
64. (original) The method of claim 34 wherein the model of the biological system includes a first set of symbols representing molecules in a first cell and a second set of symbols representing molecules in a second cell.
65. (original) The method of claim 64 wherein one or more of the first set of symbols comprises the same symbols of the second set.
66. (original) A method comprising:  
receiving a set of symbols in an inference engine, the set of symbols representing a hypothetical initial state of a biological system, the symbols representing biological elements of the system; and  
iteratively substituting at least one of the symbols by at least another symbol representing a biological element using rules that represent interactions between the biological elements until a terminal state is detected or until alternative resultant states are detected.
67. (original) The method of claim 66, further comprising outputting the terminal state or at least one of the alternative resultant states.
68. (original) The method of claim 66 wherein the hypothetical initial state represents a biological sample from a patient.
69. (original) The method of claim 68 wherein the biological sample is associated with a disease or disorder.

S/N 09/855,458  
Page 11 of 20

70. (original) The method of claim 69 wherein the disease or disorder is selected from the group consisting of cancer, diabetes, infection by a pathogen, inflammation, and a disease of aging.
71. (original) The method of claim 66, further comprising parsing a profile for a biological sample into symbols; and include at least some of the symbols in the set of symbols representing a hypothetical initial state of the biological system.
72. (original) The method of claim 66, further comprising: comparing each of the alternative resultant states to one or more reference states.
73. (original) The method of claim 72 wherein the one or more reference states comprise a state associated with cell proliferation, cell quiescence, cell apoptosis, and cell differentiation.
74. (original) The method of claim 72 wherein the alternative resultant states are compared to two or more reference states, each reference state being associated with a diagnosis.
75. (original) The method of claim 66 wherein the set of symbols representing hypothetical initial state comprises a symbol representing a genetic alteration.
76. (original) The method of claim 66 wherein one or more of the symbols representing the biological elements is typed.
77. (withdrawn) A method comprising:  
receiving into an inference engine a rule set comprising rules that express a substitution of one or more of the symbols representing biological elements by at least

S/N 09/855,458

Page 12 of 20

another symbol representing a biological element; and determining a property of the rule set.

78. (withdrawn) The method of claim 77 wherein the property comprises an indicator of whether the rules set is terminating.

79. (withdrawn) The method of claim 77 wherein the property comprises an indicator of whether the rule set includes one or more rules expressing a feedback or feedforward interaction.

80. (withdrawn) The method of claim 77 wherein the determining comprises associative-commutative matching.

81. (withdrawn) The method of claim 77 further comprising generating a decision diagram.

82. (withdrawn) A method comprising:

receiving into an inference engine (1) at least a first and a second set of symbols wherein the first set of symbols represents a hypothetical first state of a biological system, and the second set of symbols represents a hypothetical second state of the biological system, and the symbols represent biological elements of the biological system, and (2) rules that express a substitution of one or more of the symbols representing biological elements by at least another symbol representing a biological element; and

determining if one or more of the rules must be true or false for the first state to reach the second state by processing the first state using the rules.

83. (withdrawn) The method of claim 82 wherein the hypothetical first state represents a hypothetical reference sample, the hypothetical second state represents a

S/N 09/855,458

Page 13 of 20

sample associated with a disease or disorder, and a rule determined to be true identifies biological elements represented by its operands as drug targets.

84. (withdrawn) The method of claim 82, further comprising  
identifying a first profile for a first sample associated with the hypothetical first state of the biological system,  
identifying a second profile for a second sample associated with the hypothetical second state of the biological system; and  
parsing the first and second profiles to produce the first and a second set of symbols.
85. (withdrawn) The method of claim 84 wherein the first and second samples have one or more genetic alterations with respect to one another.
86. (withdrawn) The method of claim 84 in which the first and second profiles include information about mRNA expression.
87. (withdrawn) The method of claim 84 in which the first and second profiles include information about polypeptide abundance.
88. (withdrawn) The method of claim 84 in which the first and second profiles include information about polypeptide modification.
89. (withdrawn) The method of claim 84 in which the first and second profiles include information about metabolite abundance.
90. (withdrawn) The method of claim 82 in which one or more of the rules expresses concurrent state transitions.

S/N 09/855,458

Page 14 of 20

91. (withdrawn) The method of claim 82 in which at least some of the rules are not terminating.
92. (withdrawn) The method of claim 82 in which at least one of the rules represents a feedback or feedforward interaction between biological elements.
93. (withdrawn) The method of claim 82 in which at least one or more of the symbols representing the biological elements is typed.
94. (withdrawn) The method of claim 93 in which the types of symbols are organized in hierarchical classes.
95. (withdrawn) The method of claim 82 wherein the hypothetical first state represents a hypothetical reference sample, the hypothetical second state represents a sample contacted with a drug or exogenous agent, and a rule determined to be true identifies biological elements represented by its operands as drug targets.
96. (original) An article comprising machine-readable media having encoded thereon software configured to cause the processor to:
- receive a set of symbols, the set representing a hypothetical initial state of a biological system, the symbols representing biological elements of the system; and
  - iteratively substitute one or more of the symbols representing biological elements by at least another symbol representing a biological element using rules that represent interactions between the biological elements until a terminal state or until alternative resultant states are detected.
97. (original) The article of claim 96 wherein one or more of the rules comprises an operator for expressing a relationship between at least two of the biological elements, the operator conforming to associative and commutative properties.

S/N 09/855,458

Page 15 of 20

98. (original) The article of claim 96 wherein one or more of the rules expresses concurrent state transitions.
99. (original) The article of claim 96 wherein at least some of the rules are not terminating.
100. (original) The article of claim 96 wherein at least one of the rules represents a feedback or feedforward interaction between biological elements.
101. (original) The article of claim 96 wherein one or more of the rules is reflective.
102. (original) The article of claim 96 wherein one or more of the symbols representing the biological elements is typed.
103. (original) The article of claim 102 wherein the types of symbols are organized in hierarchical classes.
104. (original) The article of claim 103 wherein a symbol for one of the hierarchical classes is matched by any symbol that is a member of the hierarchical class.
105. (currently amended) The article of claim 96 wherein the software is further configured to cause the processor to:
- receive a second set of symbols for a hypothetical second state of the biological system; and compare the second set of symbols to the terminal state or to at least one of the alternative resultant states.
106. (original) An article comprising machine-readable media having encoded thereon software configured to cause the processor to:
- receive information for a first state of a biological system;
  - generate symbols representing biological elements of the system; and

S/N 09/855,458  
Page 16 of 20

iteratively substitute one or more of the symbols representing biological elements by at least another symbol representing a biological element using rules that represent interactions between the biological elements until a terminal state or until alternative resultant states are detected.

107. (original) The article of claim 106 wherein one or more of the symbols representing the biological elements is typed.

108. (original) The article of claim 106 wherein the information comprises values, each value reflecting the abundance of a biological element in the first state.

109. (original) The article of claim 108 wherein generating comprises comparing each value to a threshold parameter for the value, and generating a symbol for the biological element whose abundance is reflected by the value if the value exceeds the threshold parameter.

110. (New) The method of claim 1 further comprising detecting whether one or more rules of the model is an infinite substitution chain.

111. (New) The method of claim 110 wherein the detecting comprises commutative matching.

112. (New) The method of claim 110 wherein the detecting comprises associative matching.

113. (New) The method of claim 1 further comprising evaluating rules of the model by associative-commutative matching.

114. (New) The method of claim 1 further comprising evaluating a rule that expresses an assertion about the model of the biological system.

**S/N 09/855,458****Page 17 of 20**

115. (New) The method of claim 1 further comprising evaluating rules of the model to determine if the rules can be reduced to a unique normal form.

116. (New) The method of claim 115 wherein the evaluating comprises a Church-Rosser checker.

117. (New) The method of claim 1 wherein at least one represented element comprises a chimeric signaling molecule, a chimeric transcription factor, or an artificial promoter.

118. (New) The method of claim 1 wherein the model comprises a rule representing an element of a designed biological circuit.

119. (New) The method of claim 1 further comprising determining whether a theorem about the biological system can be proven using the rules.

120. (New) The method of claim 119 wherein the theorem is evaluated using primitive inference procedures.

121. (New) A method comprising:

generating a model of a biological system, the model comprising rules that express a substitution of at least one symbol by at least another symbol, the symbols representing a biological element, and at least some of the rules representing interactions between biological elements; and

configuring an inference engine with the rules so that the inference engine can infer alternative results by performing substitutions on symbols representing an initial hypothetical state.

122. (New) The method of claim 121 wherein the model is reflective.



S/N 09/855,458

Page 18 of 20

123. (New) The method of claim 121 wherein at least some of the rules are non-terminating.

124. (New) The method of claim 121 wherein the inference engine comprises an associative-commutative matcher.

125. (New) The method of claim 34 wherein the processing comprises indexing multiple branches of possible system evolution and exploring the multiple branches.